FACULDADE DE
CIÊNCIAS
MÉDICAS
Universidade
Nova de Lisboa

Northeastern University
College *of* Professional Studies

VALIDAÇÃO E APLICAÇÃO CLÍNICA DE UMA ESCALA DE COGNIÇÃO SOCIAL NA ESQUIZOFRENIA

VALIDATION AND CLINICAL USE OF A MEASURE OF SOCIAL COGNITION IN SCHIZOPHRENIA

João Miguel Pereira Fernandes

Trabalho de Projecto realizado no âmbito do
Research Project in fulfillment of the requirements of

MESTRADO EM INVESTIGAÇÃO CLÍNICA
CLINICAL RESEARCH MASTER

Orientadores / *Supervisors*
David Leland Roberts, Ph.D.
Miguel Xavier, Ph.D.

2013

Agradecimentos

Este Trabalho de Projecto não teria sido possível sem o apoio do Dr. Luís Sardinha, Director do Serviço de Psiquiatria do Centro Hospitalar de Lisboa Ocidental, EPE, a quem o autor agradece por lhe ter dado a conhecer a relevância da Cognição Social na compreensão, avaliação e intervenção na Esquizofrenia.

O autor deseja ainda agradecer aos Orientadores do Projecto, o Professor David Roberts (Departamento de Psiquiatria, Divisão de Esquizofrenia e Perturbações Relacionadas, Centro de Ciências da Saúde da Universidade do Texas, San Antonio, Texas, Estados Unidos) e o Professor Miguel Xavier (Departamento de Psiquiatria e Saúde Mental, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Portugal), pela sua disponibilidade contínua e assistência, apoio e orientação inestimáveis.

Por fim, o autor gostaria de agradecer aos colaboradores do Departamento de Psiquiatria da Universidade do Texas em San Antonio, com os quais teve a oportunidade de trabalhar e cujo contributo foi indispensável para a realização deste Projecto.

Acknowledgements

This Research Project would not have been possible without the support of Dr. Luís Sardinha, M.D., Director of the Psychiatry Service of the Centro Hospitalar de Lisboa Ocidental, EPE, whom the author thanks for unraveling the relevance of Social Cognition in the understanding, evaluation and intervention in Schizophrenia.

The author would also wish to thank his Project Supervisors, Professor David Roberts, Ph.D. (Department of Psychiatry Division of Schizophrenia and Related Disorders, University of Texas Health Science Center, San Antonio, Texas, United States) and Professor Miguel Xavier, Ph.D. (Department of Psychiatry and Mental Health, Nova Medical School, Lisbon, Portugal), for their continuous availability and invaluable assistance, support and guidance.

Finally, the author would like to thank the collaborators of the University of Texas at San Antonio Department of Psychiatry he had the opportunity to work with and without whom this Project would not have been viable.

Resumo

A cognição social encontra-se frequentemente alterada na esquizofrenia. Esta alteração relaciona-se com a diminuição do funcionamento social, caracterizando-se quer por défices quer por vieses cognitivos sociais. No entanto, existem poucos instrumentos fiáveis e válidos para avaliar a cognição social na esquizofrenia, nomeadamente capazes de medir os vieses cognitivos sociais e a cognição social auto-relevante. Adicionalmente, as bases biológicas da disfunção social não estão totalmente esclarecidas. Evidências recentes sugerem que o peptídeo oxitocina (OXT) influencia o funcionamento social, e que esta relação poderá ser mediada pela cognição social. Este Trabalho de Projecto descreve a contribuição do autor para o desenvolvimento e avaliação psicométrica inicial de um novo instrumento de avaliação da cognição social, e a utilidade desta escala na investigação das associações entre a OXT e a capacidade e vieses cognitivos sociais. A *Waiting Room Task* (WRT), uma escala constituída por 26 vídeos sequenciais que simulam a experiência de observar outra pessoa numa sala de espera, foi administrada num estudo transversal com 61 doentes com esquizofrenia e 20 controlos saudáveis. Observou-se uma menor capacidade cognitiva social e um aumento dos vieses cognitivos sociais nos doentes com esquizofrenia, comparativamente aos controlos. Nos controlos e doentes com delírios, o desempenho na WRT correlacionou-se significativamente com os níveis de OXT. Esta correlação não se observou nos doentes sem delírios, sugerindo que o papel da OXT na cognição social poderá encontrar-se atenuado neste grupo. Estes achados fornecem suporte inicial para a adequação da WRT como instrumento de avaliação da cognição social na esquizofrenia, podendo ainda ser útil na investigação da sua base biológica.

Palavras-Chave

Cognição Social; Esquizofrenia; Oxitocina

Abstract

Social cognition is often impaired in schizophrenia. This impairment is related to poor social functioning and is characterized by both social cognitive deficits and biases. However, there are few reliable and valid measures of social cognition in schizophrenia, particularly measures of social cognitive bias and of self-relevant social cognition. Also, the biological bases of social dysfunction are not well understood. Emerging evidence suggests that the peptide oxytocin (OXT) influences social functioning, and that this relationship may be mediated by social cognition. This Research Project describes the author's contribution to the development and initial psychometric testing of a new measure of social cognition, and the utility of this instrument to examine associations between OXT and social cognitive capacity and bias. The Waiting Room Task (WRT), a video-based test comprising 26 sequential videos simulating the experience of facing another person in a waiting room, was administered in a cross-sectional study involving 61 patients with schizophrenia and 20 healthy controls. Social cognitive capacity was lower and social cognitive bias was increased in patients with schizophrenia compared with controls. Among controls and patients with delusions, performance on the WRT was significantly correlated with OXT level. This correlation was not found in patients without delusions suggesting that OXT's role in social cognition may be blunted in this group. These findings provide initial support for the adequacy of the WRT as a measure for assessing social cognition in schizophrenia that may also be useful in understanding its biological underpinnings.

Keywords

Social Cognition; Schizophrenia; Oxytocin

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Actividades desenvolvidas no âmbito do Trabalho de Projecto

A investigação clínica é uma actividade integrante dos objectivos gerais da formação médica especializada e relevam para a avaliação dos médicos internos (Ministério da Saúde, 2011). Podendo o programa de investigação constituir um estágio específico do programa de formação da especialidade de Psiquiatria, o autor do presente Trabalho de Projecto optou por realizar um estágio em Investigação Clínica em Esquizofrenia no Departamento de Psiquiatria, Divisão de Esquizofrenia e Perturbações Relacionadas do Centro de Ciências da Saúde da Universidade do Texas em San Antonio (UTHSCSA), Texas, Estados Unidos. Esta Divisão, cuja actividade se baseia predominantemente no desenvolvimento e implementação de projectos de investigação clínica na área da esquizofrenia, é um dos centros de referência a nível mundial para o estudo da cognição social nesta doença.

A cognição social diz respeito à forma como os indivíduos reflectem acerca de si próprios e dos outros no mundo social (Penn et al., 2008). Na esquizofrenia, a cognição social relaciona-se intimamente com o funcionamento social, cuja disfunção constitui um dos critérios de diagnóstico da doença (American Psychiatric Association, 2000). A investigação em torno da cognição social na esquizofrenia operacionalizou este conceito em torno de diferentes domínios: a "percepção emocional" (a capacidade de inferir os estados emocionais dos outros), a "teoria da mente" (a capacidade de inferir os estados mentais dos outros), o "viés atributivo" (tendências individuais para explicar as causas dos eventos sociais) e "conclusões precipitadas" (tendência para retirar significados com base em elementos insuficientes) (Roberts e Velligan, 2012).

Apesar do consenso em torno da conceptualização da cognição social na esquizofrenia, subsiste a necessidade de construir instrumentos de avaliação com características psicométricas adequadas e devidamente validados que a consigam medir com fiabilidade (Savla et al., 2012). A este

respeito, importa considerar que na esquizofrenia a disfunção cognitiva social engloba tanto défices (a nível da percepção emocional e teoria da mente) como vieses cognitivos (a nível dos vieses atributivos e conclusões precipitadas); no entanto, a maior parte dos instrumentos de avaliação da cognição social na esquizofrenia actualmente disponíveis mede sobretudo os défices cognitivos, mas não os vieses cognitivos, sobretudo na sua dimensão auto-relevante (que diz respeito ao sujeito).

Durante o estágio em investigação clínica realizado, o autor teve a oportunidade de colaborar no estudo psicométrico inicial de uma nova escala de avaliação da cognição social na esquizofrenia, que atribui particular ênfase à medição dos vieses cognitivos e à auto-relevância. Esta escala, denominada *Waiting Room Task* (WRT), foi desenvolvida pelo Professor David Roberts, coorientador do presente Trabalho de Projecto. A contribuição do autor deste Projecto para a avaliação psicométrica da escala focou-se na análise estatística e interpretação dos dados derivados de um estudo transversal envolvendo 61 doentes com esquizofrenia e 20 controlos saudáveis, realizado pela Divisão de Esquizofrenia e Perturbações Relacionadas do UTHSCSA antes da chegada do autor e sem a sua participação directa. Adicionalmente, o autor reviu a literatura relacionada com a cognição social na esquizofrenia, nomeadamente no que concerne à sua avaliação clínica e impacto nas manifestações clínicas da doença. A partir deste trabalho de colaboração, o autor contribuiu para a redacção do Artigo I incluído nesta monografia, submetido à revista científica *Psychiatry Research*, e que se encontra actualmente em revisão.

A partir do mesmo estudo que permitiu colher os dados necessários à avaliação psicométrica da WRT, foram analisados outros parâmetros clínicos relevantes, como o desempenho neurocognitivo e a gravidade dos sintomas da doença, e laboratoriais, como o nível do peptídeo oxitocina (OXT), que se sabe estar implicado na mediação dos comportamentos sociais (MacDonald and MacDonald, 2010). Desta forma, foi possível

associar um potencial marcador biológico de disfunção cognitiva social ao desempenho no instrumento de avaliação recém-desenvolvido, bem como identificar relações específicas entre a OXT e dimensões particulares da cognição social na esquizofrenia. Desta investigação, para o qual o autor do presente Trabalho de Projecto contribuiu através da revisão da literatura relevante acerca do papel da OXT na cognição social, da análise estatística dos dados resultantes do estudo transversal previamente referido e da elaboração do respectivo relatório, resultou o Artigo II incluído nesta monografia, submetido e aceite para publicação pela revista científica *Schizophrenia Research*.

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Activities conducted during the Research Project

Clinical research is an activity that makes part of the general objectives of specialized medical training and that is relevant for evaluation of medical residents (Ministry of Health, 2011). Since research activities can be conducted during a specific fellowship integrated in the Psychiatry specialty training program, the author of the current Research Project as opted to participate in a Clinical Research Fellowship in the Department of Psychiatry, Division of Psychiatry and Related Disorders at the University of Texas Health Science Center, San Antonio (UTHSCSA), Texas, United States. This Division, whose activity is predominantly based on developing and implementing clinical research projects in schizophrenia, is one of the world's most recognized reference centers for the study of social cognition in this disease.

Social cognition concerns to the way individuals think about themselves and others in the social world (Penn et al., 2008). In schizophrenia, social cognition is intimately related to social functioning, whose dysfunction constitutes one of the diagnostic criteria for the disease (American Psychiatric Association, 2000). Research around social cognition in schizophrenia has operationalized this concept around different domains: "emotion perception" (the ability to infer other's emotional states), "theory of mind" (the ability to infer other's mental states), "attributional bias" (individual tendencies used to explain the causes of social events) and "jumping to conclusions" (the tendency to withdraw meanings based on insufficient evidence) (Roberts and Velligan, 2012).

Although there is consensus around the conceptualization of social cognition in schizophrenia, the need subsists for properly validated instruments with adequate psychometric characteristics that can reliably assess it (Savla et al., 2012). Within this context, it is important to consider that in schizophrenia social cognitive dysfunction comprises both cognitive deficits (in emotion

perception and theory of mind) and biases (like attributional biases and jumping to conclusions); however, most assessment instruments for social cognition in schizophrenia currently available measure mostly cognitive deficits, but not cognitive biases, particularly in their self-relevant dimension (that concerns the subject).

During his clinical research fellowship, the author had the opportunity to collaborate in the initial psychometric study of a new assessment scale of social cognition in schizophrenia, that gives particular emphasis to the measurement of cognitive biases and self-relevancy. This scale, named the Waiting Room Task (WRT), was developed by Professor David Roberts, Ph.D., co-supervisor of this Research Project. The author's contribution for the psychometric evaluation of the scale was focused on the statistical analysis and interpretation of data derived from a cross-sectional study involving 61 patients with schizophrenia and 20 healthy controls, conducted by the Division of Schizophrenia and Related Disorders at UTHSCSA prior to the author's arrival and without his direct participation. Additionally, the author reviewed the literature related to social cognition in schizophrenia, namely in what concerns its clinical evaluation and the impact on the clinical manifestations of the disease. From this collaborative work, the author contributed to the redaction of Article I included in this monograph, which was submitted to the journal "Psychiatry Research", and that is currently under review.

The same study that provided the necessary data for the psychometric evaluation of the WRT, also analyzed other relevant clinical aspects, like neurocognitive performance and disease symptoms severity, and laboratory parameters, like levels of the peptide oxytocin (OXT), that is known to be implicated in mediating social behaviors (MacDonald and MacDonald, 2010). Hence, it was possible to associate a potential biological marker of social cognitive dysfunction to performance on this recently developed assessment instrument, as well as identify specific relations between OXT and particular

dimensions of social cognition in schizophrenia. From this research, for which the author of this Research Project has contributed by reviewing the relevant literature about the role of OXT in social cognition, by analyzing the data derived from the previously mentioned cross-sectional study and by elaborating the corresponding report, resulted Article II included in this monograph, which was submitted to and accepted for publication in the journal Schizophrenia Research.

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Artigo / *Article* I. *The waiting room task: A new measure of social cognitive capacity and bias in schizophrenia*

Authors

David Leland Roberts[a*]
João Miguel Pereira Fernandes[b]
Helena Marea Service[c]
Heather Nicole Carr[a]
Cynthia Sierra[a]
Dawn Irene Velligan[a]

[a] Department of Psychiatry
Division of Schizophrenia and Related Disorders
University of Texas Health Science Center, San Antonio
7703 Floyd Curl Drive, MC 7797
San Antonio, TX 78229
phone: 210-562-5263
fax: 210-567-1291
email: robertsd5@uthscsa.edu

[b] Departamento de Psiquiatria e Saúde Mental
Centro Hospitalar de Lisboa Ocidental, EPE
Calçada da Tapada 155, 1300 Lisboa
Portugal

[C] Department of Psychology
University of Helsinki
PO Box 9 (Siltavuorenpenger 1 A)
FI-00014 University of Helsinki
Finland

Abstract

Social cognition is often impaired in schizophrenia and this impairment is related to poor functioning. However, there are few reliable and valid measures of social cognition in schizophrenia, particularly measures of social cognitive bias and of self-relevant social cognition. The authors describe the development and initial psychometric testing of a new measure of social cognition. The Waiting Room Task (WRT) is a video-based test comprising 26 sequential videos simulating the experience of facing another person in a waiting room. Eighty-one subjects (61 patients with schizophrenia or schizoaffective disorder and 20 controls) were asked to evaluate target people's gaze direction, mental state and emotional state. Within a signal detection framework, we found increased threat detection bias (P=0.005) and lower social cognitive sensitivity (P=0.002) in patients compared with controls. Social cognitive sensitivity (d') on the WRT correlated negatively with negative symptom severity (r=-0.231, P<0.05) and executive functioning (r=-0.225, P<0.05), while bias (false alarms) correlated with positive symptoms (r=0.230, P<0.05). The WRT exhibited good internal consistency. These findings provide initial support for the WRT as measure for assessing self-relevant social cognitive capacity and bias in schizophrenia.

Keywords

Emotion Perception; Theory of Mind; Attributional Bias; Gaze Detection; Self-Relevance

1. Introduction

Social cognitive dysfunction in psychiatric disorders is widespread (Derntl and Habel, 2011). In schizophrenia, it is related with poor social functioning (Couture et al., 2006). Despite its recognized importance, social cognitive dysfunction is a relatively young field of investigation with a range of problems, including inconsistency in how it is conceptualized, operationalized and measured across populations of interest and research centers (Green et al., 2008; Brunet-Gouet, 2011). For example, a distinction can be drawn between measures that conceptualize social cognition as a capacity (e.g., emotion perception, Theory of Mind [ToM]), and those that conceptualize it as a process for making judgments under uncertainty (e.g., attributional bias; jumping to conclusions bias) (Penn et al., 2008; Roberts and Pinkham, in press). A conceptual framework that integrates these approaches is needed (Green et al., 2008).

A second challenge is the lack of adequate standardization and psychometric validation of instruments (Savla et al., in press). In particular, there is a need for instruments that more cleanly differentiate between social cognition and neurocognition. Although factor-analytic studies suggest that neurocognition and social cognition are relatively independent domains (Bach et al., 2000; Havet-Thomassin et al., 2006; Sergi et al., 2007; van Hooren et al., 2008; Muller et al., 2010; Fanning et al., 2012), performance on specific social cognitive tasks has been found to be influenced by subjects' neurocognitive abilities, including verbal memory and executive functioning (Janssen et al., 2003; Bell et al., 2010). This problem is likely due, in part, to the neurocognitive load introduced by non-essential facets of the instruments being used, such as encoding and memory retrieval on verbally-presented tasks (e.g., the Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]; Mayer et al., 2002), context integration and logical reasoning on tasks such as those that require analysis and ordering of cartoon panels (e.g., ToM Picture Story Task; Brüne, 2003), and expressive language on

tasks that require sentence-form verbal responding (e.g., the Hinting task; Corcoran et al., 1995).

A third challenge is the equivocal support for the existence of social cognitive threat detection bias in schizophrenia. This bias can be conceptualized as comprising two components: a bias toward inferring self-directed intentionality and a bias toward inferring that this intentionality has a negative or hostile valence. There is evidence that some individuals with schizophrenia exhibit biases in gaze perception, memory, attention allocation, and eye movement that are consistent with a broader threat-detection bias (reviewed in Green and Phillips, 2004). However, support for such a bias in mental state inference has been equivocal (reviewed in Garety and Freeman, 1999). For example, the Ambiguous Intentions Hostility Questionnaire (AIHQ; Combs et al., 2007), perhaps the most widely used measure of this domain, frequently fails to show differences between schizophrenia and control groups, and at times shows patients to have *less* bias than do controls (Roberts and Penn, 2009). One possible reason for this problem is that patients may "fake good," disavowing hostile inference even when it is present (Corrigan et al. 1996; Roberts et al., 2009). An alternate approach to assessing inference of threat has been to measure patients' assessment of the trustworthiness and approachability of target faces. This research also has produced conflicting evidence, with one report finding that people with schizophrenia and paranoia exhibit elevated inferences of untrustworthiness (Hooker et al., 2011) and another showing a pattern of more positive trustworthiness judgments relative to controls (Baas et al., 2008). In sum, there is still equivocal evidence linking schizophrenia with a social cognitive bias toward inferring hostile, self-directed intentionality in others.

The current report describes the development and initial psychometric testing of the Waiting Room Task (WRT), an instrument designed to address the three challenges noted above. Namely, the WRT is designed to: (1)

provide integrated measurement of social cognitive capacity and social cognitive bias; (2) minimize the influence of extraneous neurocognitive factors on social cognitive performance, and; (3) provide valid assessment of threat detection bias.

2. Methods

2.1. Scale development

Design of the WRT was informed by the dual-process approach to social cognition (Chaiken and Trope, 1999) and by signal detection methodology (Corrigan and Green, 1993; Swets, 1988). The dual-process framework conceptualizes cognition as the interaction of controlled and automatic processes. Controlled processes occur under the intention, awareness, and control of the individual, and are relatively effortful, slow and easily depleted. Automatic processes occur outside of the intention, awareness, and control of the individual, are relatively effortless, fast, and abundant. Included in controlled processes are executive function, working memory, purposive memory encoding and retrieval, and aspects of verbal language production. Controlled processes are known to be relatively more impaired in schizophrenia than are automatic processes (Ragland et al., 2007). With the WRT, we sought to control for neurocognitive load by measuring aspects of social cognition that are relatively automatic, and therefore less vulnerable to diminution as a result of general controlled processing impairments.

Signal detection methodology enables the dissociation of capacity and bias processes in test responding. The WRT is designed to generate separate estimates of capacity (operationalized as *sensitivity* or *d'*) and threat detection bias (*false alarms*) in the domains of eye gaze perception, ToM, and emotion perception.

The WRT is a video-based task that simulates the experience of entering an office waiting room and encountering a seated target person, who looks up (Figure 1). The behavior of the target person is manipulated over sequential trials across three dimensions: 1) Whether the target looks directly at the subject or gazes 15 or 30 degrees to the right or left; 2) The duration of the target's gaze at or away from the subject (0.5 seconds vs. 3 seconds), and; 3) The target's expressed facial emotion (anger, happiness, sadness or no emotion), which onsets momentarily after the target person looks up, and lasts for either 0.5 or 3 seconds (yoked to gaze duration). Gaze duration is manipulated in order to influence subjects' inference of whether the target thought about whatever he or she gazed at. Onset of emotion expression occurs after the target looks up to create the impression that the emotion occurred in response to whatever the target looked at.

Response variables are the subject's judgment of: 1) Gaze direction: "Did the person look at you?" (dichotomous: yes/no); 2) ToM: "Did it seem like the person had a thought about you?" (dichotomous: yes/no), and; 3) Emotion perception: "How did the person feel?" (categorical: happy, sad, angry, no emotion).

From a preliminary set of 45 stimulus videos administered to 18 high-functioning individuals without mental illness, 26 videos were selected which yielded over 70% consensus on response variables, with a balanced distribution of easy, moderate and high difficulty items (Erwin et al., 1992). By including high difficulty items (i.e., those with only 70 to 75% consensus), we sought to increase the WRT's sensitivity to inferential bias by ensuring a sufficient degree of ambiguity in social stimuli to prevent subjects from being able to fake good by guessing normative responses. The risk of increasing ambiguity in this way is increasing the vulnerability of the WRT to low reliability and to variability across cultural sub-populations (Han, in press). To account for this risk moving forward, we reevaluate item consensus in each

new healthy control sample, and remove items that do not achieve 70% consensus.

The 26-item WRT was then studied on a clinical sample comprising 20 patients with DSM-IV-TR diagnosed schizophrenia and 10 demographically similar controls as a preliminary test of the validity of its subscales (Roberts and Hoffman, 2011). After removal of low consensus items, we examined the convergence of participants' raw gaze detection responses with correct answers. Mean accuracy score in controls was 19.13 (*SD* = 2.5) out of 21, suggesting that the scale is adequate to assess perception of eye gaze direction. The ToM subscale correlated significantly with an existing ToM scale, the Social Cognition Screening Questionnaire (full sample, r=0.409; P=0.047) (SCSQ; Roberts et al., 2012). Within the patient subgroup (n=20), this correlation remained strong at 0.388, supporting the validity of the WRT ToM subscale. Finally, regarding the emotion perception subscale, control participants exhibited ceiling effects on both this and the Face Emotion Identification Task (FEIT; Kerr and Neale, 1993). In the patient group, the WRT emotion perception scale correlated significantly with the FEIT (r=0.799; P<0.001), providing evidence of the WRT's validity as a measure of emotion perception.

Building on this initial evidence of the convergent validity of the WRT's raw scales, the current psychometric study examined the performance of the WRT in a larger sample of matched patients and controls, with emphasis on (1) its relationship to neurocognition, (2) its performance when scored using a signal detection approach, and (3) it's ability to detect threat detection bias.

2.2. Subjects

Subjects were 61 clinically stable patients with DSM-IV-TR diagnoses of schizophrenia or schizoaffective disorder (American Psychiatric Association, 2000). Twenty healthy controls were recruited from the same community. Controls were recruited to resemble the patient sample in terms of age,

gender ratio, ethnicity, and socioeconomic status. Demographically, groups differed significantly only in education (Table 1). Diagnosis of schizophrenia or schizoaffective disorder was confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Healthy controls were screened with the SCID screening interview to rule out history of mental illness and family history of psychotic disorders. Subjects were excluded if they had prior history of significant neurological disorder, head trauma, mental retardation or recent substance use.

2.3. Instruments

In addition to the WRT, social cognition was assessed with the Trustworthiness Task—Abbreviated (Adolphs et al., 1998, Couture et al., 2010), a measure of social judgment and threat detection bias. Subjects were shown 42 black-and-white faces and asked to rate them in terms of trustworthiness using a 7-point Likert scale (-3 to 3). The task was divided into two scales: the average rating on trustworthy faces and the average rating on untrustworthy faces (Couture et al., 2010).

Among patients, symptom severity was evaluated with the Brief Psychiatric Rating Scale (BPRS)—extended version (Lukoff et al., 1986), which assesses the presence and severity of 24 dimensions of psychiatric symptoms based on behavior and content during a clinical interview. A Positive Symptoms score was calculated from the sum of the Positive Symptom items of the BPRS (Anderson et al., 2004). Additionally, the Negative Symptom Assessment—16-item version (NSA-16) (Axelrod et al., 1993) was used to better characterize negative symptoms, as these have been previously linked to aspects of social cognition (Lincoln et al., 2011; Lysaker et al., in press). Total scores on the symptom scales were computed as the sum of individual items.

Neurocognition was assessed with the Hopkins Verbal Learning Test (HVLT) – Revised (Shapiro et al., 1999) which evaluates verbal memory, the Phonemic (letter) and Category (animals and occupations) tests for verbal

fluency (Joyce et al., 1996) and the Trail Making Test Parts A and B (Reitan, 1992) which evaluates executive function. Scores on the HVLT were computed as the total number of correct answers after three trials. For the verbal fluency tests, we summed the number of valid answers in each of the three tasks (letter, animal and occupations) individually. Scoring of the Trail Making Test was recorded as the total number of seconds required to complete the two successive tasks.

2.4. Procedures

Participants completed the 26-item WRT. For signal detection analysis, responses were categorized on each item pre-hoc across two dichotomies: hit (correct; bias consistent) vs. miss (incorrect, bias inconsistent) & false alarm (incorrect, bias consistent) vs. correct rejection (correct; bias inconsistent). For the gaze detection and ToM subscales, hits were defined as the correct identification of self-directed eye gaze and mental state inference respectively, and false alarms were defined as the incorrect identification of any of these when they were not in fact present. For the emotion perception subscale, hit was defined as a positive identification of the emotion anger while false alarm was defined as the incorrect identification of anger when another emotion was being expressed (Green and Phillips, 2004). On each scale, social cognitive capacity was operationalized as the sensitivity index (*d'*), which was calculated as the difference between the z-transformations of the hit rate and the false alarm rate, according to the following formula: $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$. Threat-detection bias was operationalized as the false alarm rate (Corrigan and Green, 1993). We also computed Total sensitivity and bias scores by combining the hit rates and false alarm rates across the three subscales.

Internal consistency of the WRT was tested using Cronbach's alpha, Guttman's Split-Half method and total-item correlations. Convergent and divergent validity were evaluated using Kendall's tau-b correlations (Arndt et al., 1999) between WRT measures, schizophrenia symptom scales and

neurocognitive variables in the patient group. Parametric statistical procedures were used whenever variables were normally distributed. Since most of our variables were not normally distributed we used Quade's rank analysis of covariance to examine the effects of confounders in group comparisons (Quade, 1967).

3. Results

3.1. Group differences on covariate measures

Patients differed significantly from healthy controls in education and performance on the HLVT, the Occupations Category of the Fluency Test and the Trail Making Test (Table 1). We found no differences between the two groups in performance on the Letter and Animal Category verbal fluency tests nor on the trustworthiness task, either for the trustworthy or untrustworthy faces scale.

3.2. Discriminant validity of the WRT

Performance on the WRT was significantly different between patients and healthy controls on all sensitivity (*d'*) and threat detection bias (false alarm) scales (Table 2). Significant differences in *d'* appeared to be due primarily to differences in false alarm rates as these were statistically significant for all subscales and the Total score while groups did not differ significantly in hit rates on any of the three subscales.

We repeated group comparisons controlling for potential confounders to determine if differences remained significant. After controlling for HVLT, category fluency test and education level, we obtained the following results for the sensitivity scores: 1) Gaze subscale: F=3.245, df=80, P=0.075; 2) ToM subscale: F=3.917, df=80, P=0.051; 3) Emotion perception subscale: F=4.187, df=79, P=0.044; and 4) Total score: F=4.827, df=79, P=0.031 (all Quade's test). For bias scores, the difference between groups remained

significant only for the emotion perception subscale: 1) Gaze subscale: F=2.485, df=80, P=0.119; 2) ToM subscale: F=2.313, df=80, P=0.132; 3) Emotion perception subscale: F=3.952, df=79, P=0.050; and 4) Total score: F=3.669, df=79, P=0.059 (all Quade's test). When Trail Making Test scores were included in the model, significant differences disappeared for all sensitivity and bias subscales and Total scores (all P>0.300, Quade's test).

3.3. Convergent and divergent validity of the WRT—neurocognition and symptoms

In the patient sample, none of the WRT sensitivity or bias variables was significantly correlated with the HVLT or the verbal fluency tests (Table 3). The *d'* for the emotion perception subscale and Total *d'* score were both negatively correlated with performance on the Trail Making Test, an effect that was driven by strong correlations with hit rates but not false alarm rates. In the healthy controls group, there were no significant correlations between neurocognitive measures and the signal detection variables.

There were several significant correlations between patient symptoms and WRT performance (Table 3). Regarding WRT sensitivity scores, both the ToM *d'* subscale and the Total *d'* scale were significantly correlated with negative symptoms. The Total *d'* was also negatively correlated with overall BPRS score. The gaze and emotion perception *d'* subscales did not show any significant correlations with symptom variables. Regarding WRT bias scores, the gaze and ToM scales showed significant and trend level associations, respectively, with BPRS-rated positive symptoms, while the Total bias score also showed a trend-level association with Positive symptoms.

3.4. Validity of the WRT—threat detection bias

Threat detection bias in schizophrenia is thought to be most associated with positive symptoms, especially persecutory experiences (Green & Phillips, 2004). As noted above, patients overall exhibited greater self-relevance bias

on the gaze detection, ToM, and emotion perception scales than did controls. Within the patient group, we also compared bias between those high (BPRS item 9 ≥ 4) vs. low (BPRS item 9 ≤ 3) in suspiciousness and high (BPRS item 11 ≥ 3) vs. low (BPRS item 11 ≤ 2) in delusions. The high suspiciousness group exhibited significantly greater bias on the gaze scale (Z = -2.031; P=0.042), a trend toward greater bias on the ToM scale (Z=-1.653, P=0.098), no difference on the emotion perception scale (Z=-0.187, P=0.852), and a trend toward greater bias on the Total scale (Z=-1.765, P=0.078, all Mann-Whitney U). The high delusional group exhibited no difference on bias on the gaze (Z = -1.633; P=0.103), ToM scale (Z=-1.473, P=0.141) and emotion perception (Z=-0.054, P=0.957) subscales, although there was a trend toward greater bias on the Total scale (Z=-1.784, P=0.074, all Mann-Whitney U). As noted above, all bias scales except emotion perception were correlated with positive symptoms and, as predicted, none of the WRT scales correlated significantly with either scale of the trustworthiness task.

3.5. Reliability of the WRT

The three WRT subscales correlated significantly with each other: 1) Gaze and ToM subscales: r=0.444, P<0.001; 2) Gaze and emotion perception subscales: r=0.252, P=0.002; 3) ToM and emotion perception subscales: r=0.360, P<0.001. Cronbach's alpha for all 63 items of the WRT was 0.819. For the 23 items in the gaze subscale it was 0.736, for the 19 items in the ToM subscale it was 0.555 and for the 21 items in the emotion perception subscale it was 0.652. The item-total correlation scores indicated that no individual item would increase the global alpha by more than 0.005. Using Guttman's Split-Half method we obtained a reliability coefficient of 0.800.

4. Discussion

The WRT is a new measure of social cognition designed with three aims in mind: (1) To minimize extraneous neurocognitive load; (2) To provide combined measurement of social cognitive capacity and bias; and (3) to provide valid assessment of social threat detection bias. The current study was an initial psychometric evaluation of the WRT, with emphasis on these aims.

Regarding the first aim, among patients the sensitivity and bias scales for both eye gaze and ToM showed no correlations with any neurocognitive measures, while the emotion perception sensitivity scale correlated significantly with the Trail Making Test, a measure of executive functioning. The lack of relevant associations between our ToM scales and neurocognitive measures is promising given that other widely used ToM measures have shown associations with neurocognition (e.g., Hinting task; Bell et al. 2010). We believe that the lack of association between the WRT ToM *d'* scale and neurocognitive measures is due largely to the fact that the WRT scale does not require subjects to integrate multiple sources of information, recall complex stimuli or verbal information, or use logical reasoning, and responses require only dichotomous judgments. In this sense, the WRT may be a more purely social cognitive measure of ToM than are scales that tap these neurocognitive capacities. On the other hand, the WRT operationalizes ToM in a manner very different from extant measures in the schizophrenia literature, and thus it could be argued that the WRT does not measure 'true' ToM. This argument is weakened by our initial study in which the WRT's ToM scale correlated with an established measure of ToM (Roberts and Hoffman, 2011). It is also the case that ToM is a contested construct which is operationalized in a wide range of ways, none of which is considered a 'gold standard' (Green et al., 2008). Given that the value of social cognition to schizophrenia research hinges on its link to social functioning (Couture et al., 2006), one mark of a good ToM measure should

perhaps be the strength of its link to real world social functioning. To this end, the WRT was conceptualized within an established self-regulatory model of social cognition (Rothman et al., 2004) which emphasizes the adaptive function of determining the self-relevance of the behavior of conspecifics—addressing the question, “Does this person's behavior have significance for me?” From this standpoint, determining whether another person is thinking about oneself may be more adaptively important than determining the precise contents of a person's mind. Thus, although the WRT scale may measure a restricted facet of ToM, arguably it measures an aspect that is particularly important to social functioning.

In contrast to the ToM and gaze scales, the WRT emotion perception *d'* scale was correlated with our measure of executive function. In light of the differential correlations of executive function with hit rates (significant) and false alarm rates (non-significant) it appears that executive functioning impairments affect emotion perception by lowering capacity and not by increasing bias. This finding may have resulted in part from the increased complexity introduced to this scale by subjects having to select from four response options instead of two. Alternatively, it may be that executive functioning is necessary for emotion perception judgments, as has been suggested by several studies (Bozikas et al., 2004; Pessoa, 2009).

Regarding the second aim, we applied signal detection methodology to generate separate estimates of social cognitive sensitivity and threat detection bias. Across all three domains measured, sensitivity and bias scores differentiated between controls and patients in the expected direction: Controls exhibited greater sensitivity in identifying gaze direction, thought self-referentiality, and facial emotion. Controls also exhibited significantly lower bias toward inferring self-directed gaze and thought, and toward inferring anger. Comparison of the components of the sensitivity scores suggests that across subscales lower sensitivity in patients was driven primarily by a bias toward erroneously inferring social threat (false

alarms) rather than by a failure to detect actual evidence of threat (hit rate). Although preliminary, this finding suggests that aberrations in automatic social cognitive judgments in schizophrenia may be due more to over-activation of threat detection processes rather than a breakdown in the capacity to judge others' social behavior and intentions. This finding is consistent with the gaze detection literature, which has shown that schizophrenia patients' incorrect responding is due primarily to self-referential bias rather than perceptual deficit (Hooker and Park, 2005). This finding is also consistent with research suggesting that in schizophrenia controlled processes are more deficient than automatic processes, and aberrant functioning of social neurocircuitry is characterized more by abnormal modulation rather than impaired activation (Pinkham, in press).

The third aim of the WRT was to provide valid assessment of social threat detection bias in schizophrenia. Previous research has associated schizophrenia with self-referential gaze bias, but efforts to demonstrate self-referential thought bias have been equivocal (Garety and Freeman, 1999; Green and Phillips, 2004). The WRT showed significant differences between patients and controls in both domains. Further supporting the WRT's sensitivity to threat detection bias, patients with high paranoia exhibited greater bias than did non-paranoid patients in gaze detection and, although only at a trend level, in self-referential thought detection. Also, WRT bias scales were associated with positive, but not negative, symptomatology. These findings are consistent with the theoretical association in the literature between threat detection bias and paranoia (Combs et al., 2007). In contrast to the WRT, the trustworthiness task did not differentiate between controls and patients in the current sample, suggesting that the WRT may be a more sensitive measure of threat detection bias. One possible explanation for the WRT's relative success in detecting social threat bias is that it emphasizes automatic processing by providing brief stimuli and eliciting relatively quick responding. This may minimize patients' use of controlled, strategic processing, and thus decrease instances of "faking good" or strategically

disavowing actual self-referential inferences. There is evidence that measures of threat detection which emphasize controlled processing may elicit such strategic processing, diminishing their ability to detect threat detection bias (Roberts et al., 2009, Roberts and Penn, 2009). A second explanation may be that the WRT was designed to include relatively more ambiguous stimuli which also may have prevented patients from faking good.

Further psychometric data from this study were generally positive. The significant negative correlations between performance on the WRT sensitivity scales and negative symptoms is in line with previous research (Penn et al., 2008; Lincoln et al., 2011; Lysaker et al., in press). Internal consistency of the overall WRT was good. The lower internal consistency coefficients of the subscales, ranging from 0.555 to 0.736, are similar to the ones found in ToM tasks like the Hinting Task (Corcoran et al., 1995) and emotion recognition tasks like the Face Emotion Identification Test (Kerr and Neale, 1993; Roberts and Penn, 2009). Internal consistency of measures remains a challenge in this research area. One contributor to the mediocre internal consistency of the WRT ToM scale may be the relatively high ambiguity of the items. Thus, it may be difficult to develop measures that are sensitive to social cognitive bias without sacrificing some amount of reliability.

This study has several limitations. First, controls had significantly greater educational attainment than patients, a difference that may have contributed to group differences in social cognitive performance. Second, sample size was relatively small, especially in the control group. Future research with the WRT will need to use larger samples. Third, more work is needed to establish the psychometrics of the WRT, especially in the areas of convergent validity and test-retest reliability.

Further research with the WRT is warranted to test its reliability in different psychiatric disorders known to have impaired social cognition, like bipolar

disorder (Cusi et al., in press) or borderline personality disorder (Preißler et al., 2010). The WRT may also have promise for use in neuroimaging research because of its administration design and the known dissociation in neural functioning between automatic and controlled social cognition (Lieberman, 2007; Pinkham, in press). Because of the WRT's emphasis on threat detection and self-referentiality, we are also examining its association with biological measures of self-regulation, including immune markers and oxytocin.

In sum, the WRT is a new measure of social cognition in schizophrenia that takes a novel approach to addressing existing problems in the literature. Through use of signal detection methodology, dual-process theory and a self-regulatory conceptualization of social cognition, the WRT is designed to evaluate the presence of biases and deficits in social cognition. Initial testing suggests that the WRT is a valid and internally consistent measure. Findings also suggest that patients have abnormalities in automatic gaze detection and ToM, and that these abnormalities may be due more to a self-referential bias than to social cognitive deficits. These findings support ongoing development of the WRT and other applications of dual-process, signal detection, and self-regulatory approaches to the study of social cognition in schizophrenia.

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Table 1. Demographic and clinical characteristics of Patients and Controls

Variable	Patients (N=61)		Controls (N=20)	
	N	%	N	%
Gender				
- Male	46	75.41	14	70.00
- Female	15	24.59	6	30.00
Ethnicity				
- European American	9	14.75	4	20.00
- African American	40	65.57	13	65.00
- Hispanic American	12	19.67	3	15.00
Diagnosis				
- Schizophrenia	37	60.66	-	-
- Schizoaffective	24	39.34	-	-
	Mean	SD	Mean	SD
Age (years)	41.92	10.84	39.65	11.55
Education (years)[a]	11.36	2.13	12.65	1.14
HVLT[b]	17.48	5.97	22.00	4.50
Verbal Fluency				
- Letter	32.57	12.13	32.20	11.31
- Category (Animals)	15.70	7.03	18.35	3.79
- Category (Occupations)[c]	11.59	4.69	14.15	3.82
Trail Making Test				
- Seconds (Parts A + B)[d]	180.04	57.64	97.89	28.10
Trustworthiness Task				
-Trustworthy faces	0.82	1.20	0.82	1.29
- Untrustworthy faces	-0.63	1.01	-0.85	1.00
BPRS Sum Score	48.66	10.71	-	-
NSA-16 Sum Score	42.82	10.55	-	-

SD: standard deviation; HVLT: Hopkins Verbal Learning Test, revised version; BPRS: Brief Psychiatric Rating Scale, extended version; NSA-16: Negative Symptom Assessment, 16-item version.

[a] Significantly different between groups (Z=-2.561, P=0.010, Mann-Whitney U test).

[b] Significantly different between groups (t=3.108, df=79, P=0.003, t-test).

[c] Significantly different between groups (t=2.212, df=79, P=0.030, t-test).

[d] Significantly different between groups (t=-8.087, df=72, P<0.001, t-test).

Table 2. Performance on the Waiting Room Task of Patients and Controls

Variable	Patients (N=61)		Controls (N=20)	
	Mean	SD	Mean	SD
Hit Rate				
- Gaze Subscale	0.91	0.13	0.97	0.04
- ToM Subscale	0.72	0.24	0.80	0.20
- Emotion Subscale	0.77	0.20	0.84	0.16
- Total Scale[a]	0.83	0.13	0.89	0.08
False Alarm Rate				
- Gaze Subscale[b]	0.27	0.30	0.12	0.18
- ToM Subscale[c]	0.23	0.22	0.10	0.13
- Emotion Subscale[d]	0.06	0.08	0.02	0.05
- Total Scale[e]	0.16	0.15	0.07	0.08
WRT *d'*				
- Gaze Subscale[f]	-0.25	1.54	0.78	0.63
- ToM Subscale[g]	-0.23	1.21	0.71	0.99
- Emotion Subscale[h]	-0.18	1.38	0.62	1.03
- Total Scale[i]	-0.27	1.42	0.90	0.87

SD: standard deviation; ToM: Theory of Mind; WRT: Waiting Room Task.

[a] Significantly different between groups (Z=-2.136, P=0.033, Mann-Whitney U test).

[b] Significantly different between groups (Z=-2.267, P=0.023, Mann-Whitney U test).

[c] Significantly different between groups (Z=-2.363, P=0.018, Mann-Whitney U test).

[d] Significantly different between groups (Z=-2.169, P=0.030, Mann-Whitney U test).

[e] Significantly different between groups (Z=-2.785, P=0.005, Mann-Whitney U test).

[f] Significantly different between groups (Z=-2.531, P=0.011, Mann-Whitney U test).

[g] Significantly different between groups (t=3.177, df=79, P=0.002, t-test).

[h] Significantly different between groups (Z=-2.422, P=0.015, Mann-Whitney U test).

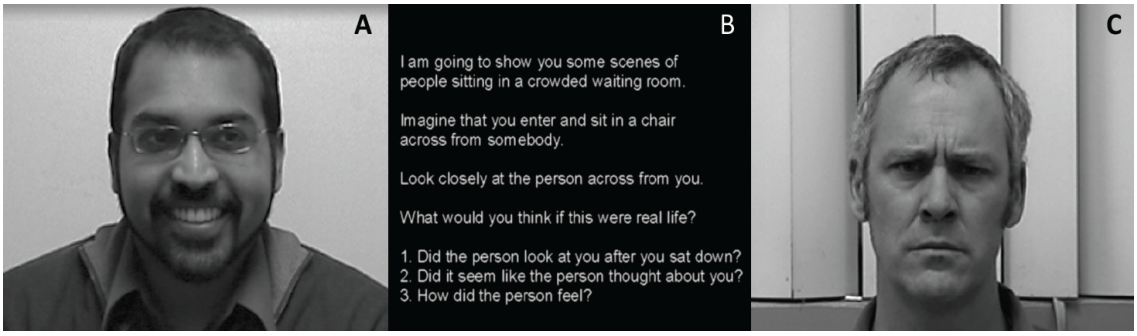
[i] Significantly different between groups (Z=-3.167, P=0.002, Mann-Whitney U test).

Table 3. Correlations between WRT and Symptom and Cognitive Scales (Patient Sample)

	BPRS	BPRS Pos.	NSA-16	HVLT	Letter VF	Trail Making Test
Hit Rate						
- Gaze Subscale	0.012	-0.033	-0.041	0.068	0.121	-0.157
- ToM Subscale	-0.057	-0.054	**-0.320*** **	0.141	0.126	**-0.215***
- Emotion Subscale	-0.017	-0.035	**-0.247****	0.081	0.192*	**-0.269****
- Total Scale	-0.070	-0.103	**-0.330*** **	0.131	0.219*	**-0.317*** **
False Alarm (Bias)						
- Gaze Subscale	**0.248****	**0.232***	0.030	-0.057	-0.020	0.062
- ToM Subscale	0.130	0.179	-0.013	-0.098	-0.030	0.099
- Emotion Subscale	0.157	0.053	-0.098	-0.048	-0.033	0.012
- Total Scale	**0.210***	**0.230***	0.013	-0.98	-0.075	0.110
WRT *d'* (sensitivity)						
- Gaze Subscale	-0.139	-0.115	-0.095	0.124	0.065	-0.133
- ToM Subscale	-0.149	-0.134	**-0.254****	0.111	0.067	-0.148
- Emotion Subscale	-0.155	-0.064	-0.116	0.087	0.180	**-0.223***
- Total Scale	**-0.178***	-0.154	**-0.231***	0.135	0.162	**-0.225***

BPRS: Brief Psychiatric Rating Scale; BPRS Pos.: BPRS Positive Symptoms Subscale; NSA-16: Negative Symptom Assessment – 16 Items; HVLT: Hopkins Verbal Learning Test; VF: Verbal Fluency; ToM: Theory of Mind; WRT: Waiting Room Task. Kendall's tau-b correlations. * $P<0.05$, ** $P\leq0.010$, *** $P\leq0.001$

Figure 1. Example of the Waiting Room Task. A: Video showing averted eye gaze and expression of happiness; B: Instructions provided to participants during the task; C: Video showing direct eye gaze and expression of anger.



Artigo / *Article* II. *Differential correlations between plasma oxytocin and social cognitive capacity and bias in schizophrenia*

Authors

Consuelo Walss-Bass[a]
João M. Fernandes[b,*]
David L. Roberts[a]
Helena Service[c]
Dawn Velligan[a]

[a] Department of Psychiatry
Division of Schizophrenia and Related Disorders
University of Texas Health Science Center, San Antonio
7703 Floyd Curl Drive, MC 7797
San Antonio, TX 78229

[b] Departamento de Psiquiatria e Saúde Mental
Centro Hospitalar de Lisboa Ocidental, EPE
Calçada da Tapada 155, 1300 Lisboa
Portugal
phone: +351 919 773 756
fax: +351 211 454 952
email: joao.fernandes@medtools.pt
* Corresponding author

[C] Department of Psychology
University of Helsinki
PO Box 9 (Siltavuorenpenger 1 A)
FI-00014 University of Helsinki
Finland

Abstract

Social cognitive impairment is related to poor social functioning in schizophrenia. This impairment includes both deficits in emotion perception and theory of mind (ToM), and cognitive biases including attributional bias and jumping to conclusions. Oxytocin (OXT) is a hormone that has been implicated in human social behavior, and that has also been associated with regulation of inflammation. In a cross-sectional study involving 60 patients with schizophrenia and 20 healthy controls, we examined associations between OXT and social cognitive capacity and bias. Secondary analyses examined associations between OXT and inflammation. We found significant correlations between OXT and social cognitive bias in the control group and in patients with delusions, but not in patients without delusions. Social cognitive capacity only correlated significantly with OXT in patients with delusions. A correlation between OXT and inflammation was observed only in patients without delusions. Findings suggest that OXT may be implicated in social cognition both in controls and in patients with delusions, but that this association may be blunted in patients without delusions. Inflammation appears to be related to OXT rather independently of social cognition. Future longitudinal and intervention studies with OXT are needed to clarify causality in the identified associations.

Keywords

Oxytocin; schizophrenia; social cognition; inflammation; cytokines/chemokines

1. Introduction

Poor social functioning is a hallmark of schizophrenia, and research suggests that it may be due in part to social cognitive impairments (Couture et al., 2006; Fett et al., 2011). Social cognition in schizophrenia is a multidimensional construct (Mancuso et al., 2011) comprised of several different deficits and biases. Areas of deficit include emotion perception (the ability to identify others' emotional states) and theory of mind (ToM; the ability to infer others' mental states and intentions), while biases include self-referential bias (the tendency to infer others as looking at [Hooker and Park, 2005] and/or harboring intentions toward oneself [Combs et al., 2009]) and jumping to conclusions bias, among others (Penn et al., 2008). The extant literature suggests that social cognitive deficits are pervasive in schizophrenia whereas biases may be more pronounced in the subset of schizophrenia patients who have delusions (Bentall and Fernyhough, 2008; Martin and Penn, 2002). However, there is a need for improved understanding of the relationship between social cognitive deficit and bias in schizophrenia (Green et al., 2008).

Oxytocin (OXT) is a nonapetide hormone produced in the brain that has been implicated in social behavior (Churchland and Winkielman, 2012) and social cognitive functions including emotion perception, trust and social coping (Rosenfeld et al., 2010). Although most studies support OXT's prosocial effects (Macdonald and Macdonald, 2010), some studies have shown that OXT's effects may depend on social context, promoting affiliative behaviors like cooperation, generosity and trust towards in-group members while also motivating out-group derogation as evidenced by decreased adherence to fairness norms and low cooperation towards those perceived as not belonging to one's group (De Dreu et al., 2011; Radke and de Bruijn, 2012).

Because of its link to social functioning, OXT has gained increasing attention in schizophrenia research. Several studies measuring OXT or its binding

protein in plasma and cerebrospinal fluid have shown increased baseline levels in schizophrenia (Legros et al., 1992; Beckmann et al., 1985; Linkowski et al., 1984) while others have shown levels that are decreased (Keri et al., 2009; Goldman et al., 2008) or commensurate with healthy controls (Glovinsky et al., 1994). OXT plasma levels are assumed to strongly correlate with its relevant brain levels (Curchland and Winkielman, 2012; Macdonald and Feifel, 2012) and a number of studies have reported correlations between peripheral levels of OXT and behavior in schizophrenia (reviewed in Meyer-Lindenberg et al. 2011). Preclinical data from animal models of schizophrenia have shown reversal of social cognitive deficits and antipsychotic-like effects in response to OXT administration (Caldwell et al., 2009; Lee et al., 2005). In patients with schizophrenia, several trials have reported improvements in social cognitive deficits and classical psychiatric symptoms after administration of intranasal OXT (Averbeck et al., 2012; Feifel et al., 2010; Pedersen et al., 2011). However, studies of endogenous OXT levels have been more equivocal, with one study reporting a negative correlation between CSF OXT and negative symptoms (Sasayama et al., 2012) and another reporting a negative correlation between blood plasma level of OXT and both positive and general symptoms, but only in women (Rubin et al., 2010). Similarly, this research group found links between blood plasma level of OXT and emotion perception in healthy controls and females with schizophrenia, but not in ill males (Rubin et al., 2011). Finally, despite evidence that OXT plays a role in mediating in-group/out-group bias in healthy individuals, but there has been limited research on OXT and social cognitive bias in schizophrenia.

In addition to its role in social behavior, OXT has also been associated with regulation of inflammation. Preclinical studies have shown OXT to have anti-inflammatory properties that include deceleration of atherosclerotic inflammation (Ahmed and Elosaily, 2011; Szeto et al., in press). In humans, OXT has been shown to have anti-inflammatory properties in cultured vascular cells (Szeto et al., 2008) and to decrease neuroendocrine and

cytokine activation after administration of bacterial endotoxin (Clodi et al., 2008). Since increased inflammatory response has been consistently shown in patients with schizophrenia (Meyer et al., 2011; Miller et al., in press), we hypothesized inflammation could be implicated in the relationship between OXT and social cognition in schizophrenia.

In the present study we sought to identify relevant associations between OXT and both social cognitive capacity and bias. A secondary aim was to examine the potential role of inflammation in these processes.

2. Materials and Methods

2.1. Subjects

Sixty patients with DSM-IV-TR diagnoses of schizophrenia or schizoaffective disorder (American Psychiatric Association, 2000) were enrolled. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Twenty demographically matched healthy controls were recruited from the same community and screened with the SCID screening interview to rule out history of mental illness and family history of psychotic disorders. Subjects were excluded if they had prior history of significant neurological disorder, head trauma, mental retardation or recent substance use. The study was approved by the University of Texas Health Science Center at San Antonio Institutional Review Board and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Procedures

We conducted an observational, cross-sectional study in which all participants first provided a blood sample for assay of OXT and inflammatory markers and then completed social cognitive and neurocognitive tests and symptom rating interviews.

2.2.1. Blood measurements

Fasting blood was drawn by venipuncture from each subject. Blood samples were immediately processed by centrifugation at 3400 rpm for 10 min and plasma was separated into aliquots and stored at -80 oC until biological measurements were performed. One hundred μl of plasma was used for measurement of OXT levels using the Oxytocin ELISA kit from Enzo Life Sciences (cat# ADI-900-153) and following manufacturer's instructions. This assay was selected because of its high sensitivity (<12 pg/ml) and because it does not detect vasopressin, providing confidence in the results. It has been previously validated and utilized extensively in studies detecting oxytocin from human samples (Dai et al., 2012; Sasayama et al., 2012). Samples were run in duplicate, un-extracted, diluted 1:1 in dilutent provided by the kit. Fifty μL of plasma was used for detection of levels of 39 inflammatory markers using bead-based flow immunoassays from Millipore in a Luminex 100 system. These multiplex microbead assays measure protein levels with sensitivity and range comparable to standard sandwich ELISA. A subset of nine inflammatory markers (interleukin-1β [IL-1β], IL-1 receptor antagonist [IL-1RA], IL-2, soluble IL-2 receptor [sIL-2R], IL-6, IL-8, IL-10, tumor necrosis factor-α [TNF-α] and interferon-γ [IFN-γ]) was chosen for principal component analysis (PCA) based on previous studies evidencing their implication in inflammatory processes in schizophrenia (Potvin et al. 2008; Meyer et al., 2011).

2.2.2. Social cognition assessment

Social cognition was assessed with the Waiting Room Task (WRT) (Roberts et al, under review), which is designed to assess both social cognitive capacity and self-referential bias in schizophrenia. Participants view 26 brief videos simulating the experience of facing an unknown person in a waiting room. Across videos, the target person varies the direction of gaze (at or away from the camera), duration of gaze, and facial expression. For each video, the subject makes dichotomous judgments of gaze direction (whether the person looks directly at the subject or not) and ToM (whether or not it

seemed that the person had a thought about the subject). Accuracy of gaze responses is determined objectively. Accuracy of ToM responses is determined based on normative consensus from previous norming samples (Roberts et al., under review), following conventions of similar measures (Mayer et al., 2003). Scoring of WRT responses enables the dissociation of capacity and self-referential bias parameters by measuring accuracy (percent correct answers; higher indicates better performance) and false alarm rates (percent endorsement of self-referentiality on non-self-referential items; higher indicates worse performance), yielding the following four variables:

1) Gaze accuracy: correctly identified direct gazes;
2) ToM accuracy: correctly identified self-referential thought;
3) Gaze bias: incorrectly identified away gazes as direct; and
4) ToM bias: incorrectly identified non self-referential thought as self-referential.

2.2.3. Neurocognitive assessments

Regarding neurocognition, verbal memory was assessed with the Hopkins Verbal Learning Test (HVLT) – Revised (Shapiro et al., 1999) and verbal fluency was assessed using Phonemic (letter) and Category (animals and occupations) tests (Joyce et al., 1996). HVLT scores were computed as the total number of correct answers after three sequential trials. For verbal fluency tests, we considered the total number of valid answers in each of the three tasks (letter, animal and occupations) separately. Executive function was evaluated with the Trail Making Test Parts A and B (Reitan, 1992), for which a total score was recorded as the seconds required to complete both parts.

2.2.4. Psychiatric assessments

In patients, symptom severity was evaluated using the Brief Psychiatric Rating Scale (BPRS)—extended version (Lukoff et al., 1986) and the Negative Symptom Assessment—16-item version (NSA-16) (Axelrod et al.,

1993). For both scales, total scores were computed as the sum of individual items scores. Because self-relevant biases in schizophrenia have been found primarily among patients with delusions (Fine et al., 2007), Item 11 of the BPRS ("Unusual Thought Content") was used to classify patients as having delusions (scores 3 to 7) or not (scores 1 or 2).

2.3. Statistical Analyses

Dependent variables were tested for normality and skewness before further statistical analyses. Two-group comparisons (i.e., patients vs. controls; delusional vs. non-delusional patients) were performed using independent samples t-tests or, if the dependent variable was not normally distributed, Mann-Whitney U tests. Three-group comparisons were performed using Kruskal-Wallis tests since assumption of normality was not met for any of the dependent variables. Correlations between OXT levels and social cognitive measures and between OXT and inflammatory marker levels were tested using Kendall's tau-B correlation coefficients. PCA followed by a varimax rotation was used to reduce the 9 inflammatory markers into a smaller number of components accounting for most of the variance in the inflammatory variables. Factors were retained if eigenvalues were ≥ 1, and the scree plot was examined to confirm factor selection. Loadings ≥ 0.6 were used to identify the variables comprising a component. Factor scores derived from PCA were used for correlations with OXT levels and social cognitive variables.

3. Results

Patients and controls differed significantly in terms of education and performance on the HVLT, Category Verbal Fluency Tasks and Trail Making Test (Table 1).

Based on the “Unusual Thought Content” item of the BPRS, we classified 21 patients as having clinically significant delusions, and 39 as non-delusional. Patients without delusions scored lower on the BPRS (mean = 46.44 [SD = 9.98] vs. 53.71 [9.98], Z=-2.483, p=0.013) and NSA-16 (41.13 [9.53] vs. 46.76 [11.19], Z=-2.025, p=0.043) scales. They also performed better on neurocognitive measures than did patients with delusions: 1) HVLT: mean = 18.97 (6.15) vs. 14.43 (SD = 4.39), t=2.995, p=0.004; 2) Letter fluency: 34.79 (13.35) vs. 28.15 (8.34), Z=-1.835, p=0.066; 3) Animal category fluency: 17.28 (7.26) vs. 12.52 (5.59), Z=-2.533, p=0.011; 4) Occupations category fluency: 12.15 (4.79) vs. 10.38 (4.42), Z=-1.454, p=0.146; and 5) Trail Making Test: 165.24 (56.15) vs. 213.76 (48.92), t=-3.076, p=0.003.

Table 2 depicts three group comparisons for performance on the WRT and plasma OXT levels. Controls performed significantly better than the full patient group on the WRT: 1) Gaze capacity: Z=-2.798, p=0.005; 2) Gaze bias: Z=-2.343, p=0.019; 3) ToM capacity: -3.260, p=0.001; and 4) ToM bias: Z=-2.463, p=0.014. Controls also performed significantly better than each patient subgroup on all WRT variables and we found no significant differences in WRT scores between patients with and without delusions. Levels of OXT were significantly lower in controls compared to patients without delusions (Z=-2.658, p=0.008) who, in turn, had significantly lower levels of OXT than did patients with delusions (Z=-2.085, p=0.037). There was no difference in OXT levels between patients with schizophrenia and schizoaffective disorder (Z=-1.192, p=0.233) and between different antipsychotic medications (X^2=2.299, p=0.681, Kruskal-Wallis test). Also, no significant correlations were found between neurocognitive measures and any of the WRT measures and between neurocognitive measures and OXT levels.

Social cognitive capacity and bias were strongly correlated in all three groups, for both subscales (Table 3, top). Although we did not find significant correlations between OXT and social cognitive measures using the full

patient group, we found significant positive correlations between OXT and ToM bias and significant negative correlations between OXT and both gaze and ToM capacity in patients with delusions (Table 3, middle). No significant correlations were identified between OXT and any of the social cognitive capacity or bias subscales in patients without delusions. In controls, significant correlations were found between OXT and social cognitive bias, but not between OXT and social cognitive capacity.

We found no significant differences in inflammatory marker levels between the three groups (data not shown). PCA revealed the presence of two factors: 1) Factor 1 included IL-2, IL-6, IL-8, TNF-α and IFN-γ, and accounted for 48.59% of the total variance; 2) Factor 2 included IL-1β, IL-1RA, sIL-2R and IL-10, and accounted for 28.78% of the total variance. Factor 1 was significantly positively correlated with OXT in patients without delusions, but was uncorrelated with OXT in controls and in patients with delusions (Table 3, bottom). In patients without delusions, inflammation was uncorrelated with WRT performance, but significant correlations were found between Factor 1 and ToM capacity in the control group ($r=-0.462$, $p=0.007$) and Factor 2 and ToM bias in patients with delusions ($r=0.395$, $p=0.017$, not significant after Holm-Bonferroni correction [adjusted alpha = 0.013]).

4. Discussion

Our results are in line with previous studies that found social cognition to be impaired in schizophrenia (Penn et al., 2008). Patients with schizophrenia evidenced significantly lower capacity and higher bias compared to controls, both in gaze direction and ToM tasks. Interestingly, we found no differences in social cognitive capacity and bias scores between patients with and without delusions. The existence of deficits across schizophrenia subgroups is consistent with previous research (Mehl et al., 2010). Previous research on bias in schizophrenia has been somewhat equivocal, with some studies

showing exaggerated bias in the subset of patients with delusions (Combs et al., 2007; Martin and Penn, 2002) and others failing to show consistent bias in any subgroups (reviewed in Garety and Freeman, 1999; Menon et al., in press; So et al., 2012).

The present study found increased plasma levels of OXT in patients with schizophrenia compared to controls. In the patient group, OXT was significantly increased in those with delusions compared to those without. This suggests an association between OXT secretion in the brain and delusional status. Taking into account the recent data suggesting beneficial effects of intranasal OXT on classical schizophrenia symptoms (Feifel et al., 2010; Pedersen et al., 2011) and findings that show increased secretion of OXT after neuroleptic treatment (Beckmann et al., 1985) or electroconvulsive therapy (Smith et al., 1994), our findings are consistent with the view that OXT may be physiologically secreted in response to the presence of significant delusional symptoms. Unfortunately, we are unable to draw strong conclusions regarding this hypothesis due to the cross-sectional design of the current study.

Research on self-referential bias tends to focus on persecutory/paranoid delusions (Bentall and Fernyhough, 2008; Martin and Penn, 2002). Since BPRS's item 11 does not characterize delusional theme, we conducted post-hoc analyses with alternative items that could point to dominant delusional themes, like Suspiciousness or Grandiosity, but neither associated with significant OXT – social cognition correlations. The finding of a correlation between OXT and social cognitive bias both in controls and patients with delusions supports a general role for OXT in social cognition not limited to schizophrenia. This is consistent with the fact that OXT is thought to mediate social behaviors such as attachment, pair-bonding or social recognition in humans without mental disorders (Kumsta and Heinrichs, in press). The absence of a correlation between OXT and social cognitive capacity or bias in patients without delusions suggests a third factor may buffer this

association. Although the present study does not allow for a clarification of this finding, it may be related with the effective therapeutic control of delusions. However, the absence of significant delusional symptoms does not correspond to better social cognitive skills, as patients in our study without delusions performed as badly as those with delusions on the WRT. This finding is concordant with a systematic review that found that antipsychotic treatment did not change "jumping to conclusions" bias (So et al., 2010), and suggests that different approaches are needed to address social cognition and classical schizophrenia symptoms.

Unlike previous findings (Meyer et al., 2011; Miller et al., in press), we found no differences in levels of inflammatory markers between patients and controls. Our finding may be due in part to the fact that antipsychotic agents are known to decrease inflammatory markers (Kowalski et al., 2001; Zhang et al., 2004), and all patients in the current study were treated with antipsychotic medication. We did find inflammatory factor 1 (comprising IL-2, IL-6, IL-8, TNF-α and IFN-γ) to be positively correlated with OXT in patients without delusions. One possible explanation for this finding is that effective treatment of delusions may dampen the link between OXT and social cognition, leaving OXT action to be guided more by inflammatory status, which is a known promoter of endogenous OXT secretion in rats (Carvalho Borges et al., 2006) and the human amnion (Terzidou et al., 2011). This hypothesis is also supported by the lack of correlation between social cognitive performance and inflammation in the non-delusional group, suggesting that social cognition and inflammation are at least partially independent in their relation to the OXT system. However, the extent of OXT's role in inflammation in humans is not yet fully understood, so our interpretation of these findings needs to be confirmed in more oriented investigation.

Our findings support the view that OXT may exert some of its social behavior effects through bias modulation rather than by improving social cognitive

capacity. Again, the nature of cross-sectional data limit our ability to address causal hypotheses suggested by these findings: Is OXT secreted in response to increased bias-related stress or is it instead promoting self-referential social cognitive bias in healthy controls and in patients with delusions? The first hypothesis may be explained by the arguments delineated above; however, we have not studied specific psychometrical or clinical-pathological measures for stress to either support or refute this hypothesis. The second hypothesis may help to explain the paradoxical evidence that whereas most patients with schizophrenia appear to have deficits in ToM, those with delusions in some studies seem to have "hyper ToM" (Abu-Akel and Bailey, 2000; Montag et al. 2011).

Within this context, we favor a model in which OXT level is correlated with the experience of salience in the self-other connection. Increasing this experience, as through OXT administration, leads to increased mentalization, and thus may improve performance on capacity-based measures of social cognition (e.g., ToM Picture Story Task; Brüne, 2003) that utilize third-person stimuli. However, when social stimuli are self-relevant, increased mentalization is likely to increase any inherent social cognitive biases that the participant already has. That is, if a person's typical mentalizing already includes a distortion, increasing mentalizing activity will not correct this distortion, but will instead increase this distortion proportionately with the amount of increased mentalization activity. This should mean that OXT levels will be correlated with the degree of manifestation of both normative biases in healthy samples, such as preference for in-group over out-group (De Dreu et al., 2011), as well as pathological biases, such as hostile attributional bias.

A limitation of this study concerns heterogeneity of the patient sample, with a balanced mix of patients with schizophrenia and schizoaffective disorder. This aspect may be relevant in light of evidence showing altered levels of OXT in depression (Ozsoy et al., 2009; Parker et al., 2010) and of OXT's

carrier in bipolar disorder (Linkowski et al., 1984). Similarly, one study has shown different antipsychotics may ellicit different OXT stimulation patterns, with olanzapine and clozapine associating with increased stimulation (Kiss et al., 2010). However, we found no significant differences in OXT levels between patients with schizophrenia and schizo-affective disorder or between patients treated with different antipsychotic medications. As discussed previously, another limitation pertains to its cross-sectional data. This type of design does not allow conclusions regarding causal relations and calls for the need for further longitudinal studies. Based on our findings, we suggest that future research on OXT should attempt to clarify the mechanisms behind its social cognitive effects. In particular, future intervention trials may benefit by considering the effects of OXT administration on social cognitive bias in schizophrenia.

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Table 1. Demographic and clinical characteristics of Patients and Controls

Variable	Patients (N=60)		Controls (N=20)	
	N	%	N	%
Gender				
- Male	45	75.00	14	70.00
- Female	15	25.00	6	30.00
Ethnicity				
- European American	9	15.00	4	20.00
- African American	39	65.00	13	65.00
- Hispanic American	12	20.00	3	15.00
Diagnosis				
- Schizophrenia	36	60.00	-	-
- Schizoaffective	24	40.00	-	-
	Mean	SD	Mean	SD
Age (years)	42.10	10.84	39.65	11.55
Education (years)[a]	11.32	2.12	12.65	1.14
HVLT[b]	17.38	5.98	22.00	4.50
Verbal Fluency				
- Letter	32.54	12.24	32.20	11.31
- Category (Animals)[c]	15.62	7.06	18.35	3.79
- Category (Occupations)[d]	11.53	4.70	14.15	3.82
Trail Making Test				
- Seconds (Parts A + B)[e]	180.24	58.15	97.89	28.10
BPRS Sum Score	48.98	10.49	-	-
NSA-16 Sum Score	43.10	10.41	-	-

SD: standard deviation; HVLT: Hopkins Verbal Learning Test, revised version; BPRS: Brief Psychiatric Rating Scale, extended version; NSA-16: Negative Symptom Assessment, 16-item version; [a] $Z=-2.682$, $p=0.007$; [b] $t=3.165$, $p=0.002$; [c] $Z=-2.444$, $p=0.015$; [d] $t=2.251$, $p=0.027$; [e] $t=-8.023$, $p<0.001$.

Table 2. Social cognitive performance, oxytocin and inflammatory markers in Controls and in Patients with and without delusions

Variable	Controls (n=20)		Patients without delusions (n=39)		Patients with delusions (n=21)		
	Mean	SD	Mean	SD	Mean	SD	p-values*
Capacity (%)							
- Gaze	94.13	5.33	85.84	13.03	84.47	12.19	0.016
- ToM	85.53	10.65	75.30	14.80	72.43	9.97	0.003
Bias (%)							
- Gaze	12.14	18.12	25.27	31.17	31.97	27.07	0.024
- ToM	10.45	13.28	21.68	24.11	26.84	18.51	0.013
Oxytocin (pg/ml)	199.33	119.42	262.78	101.77	353.31	172.21	0.001

SD: standard deviation; ToM: theory of mind; * All Kruskal-Wallis (three group) tests

Table 3. Correlations of social cognitive capacity and bias (top), of oxytocin with social cognitive performance (middle) and of oxytocin with inflammation (bottom) in controls and in patients with and without delusions

Variable	Controls (n=20)		Patients without delusions (n=39)		Patients with delusions (n=21)	
	r	p*	r	p*	r	p*
Capacity-Bias Correlations						
- Gaze	-0.716	<0.001	-0.606	<0.001	-0.707	<0.001
- ToM	-0.523	0.005	-0.548	<0.001	-0.450	0.010
Capacity-Oxytocin Correlations						
- Gaze	-0.136	0.438	-0.058	0.622	**-0.320**	**0.050**
- ToM	-0.304	0.074	-0.047	0.686	**-0.514**	**0.002**
Bias-Oxytocin Correlations						
- Gaze	**0.472**	**0.009**	0.018	0.880	0.170	0.308
- ToM	**0.434**	**0.015**	-0.082	0.487	**0.548**	**0.001**
Oxytocin-Inflammatory Factor Correlations						
- Factor 1	0.284	0.080	**0.382**	**0.001**	-0.091	0.566
- Factor 2	-0.189	0.243	0.066	0.553	0.196	0.215

ToM: theory of mind; * All Kendall's Tau-b correlations.